

# Is the Septic Response Good or Bad?

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**Current Infectious Disease Reports** 2007, 9:366–373  
Current Medicine Group LLC ISSN 1523-3847  
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A careful balance between the inflammatory and anti-inflammatory response is vital in order to survive the daily invasion of pathogens. Sepsis has always been regarded as the result of an exacerbated detrimental inflammatory response towards invading bacteria. However, recent insights have forced us to rethink this sepsis paradigm. This review discusses the latest trends and developments in the sepsis field and helps to set the stage for the current debate on whether the sepsis response is good or bad.

## Introduction

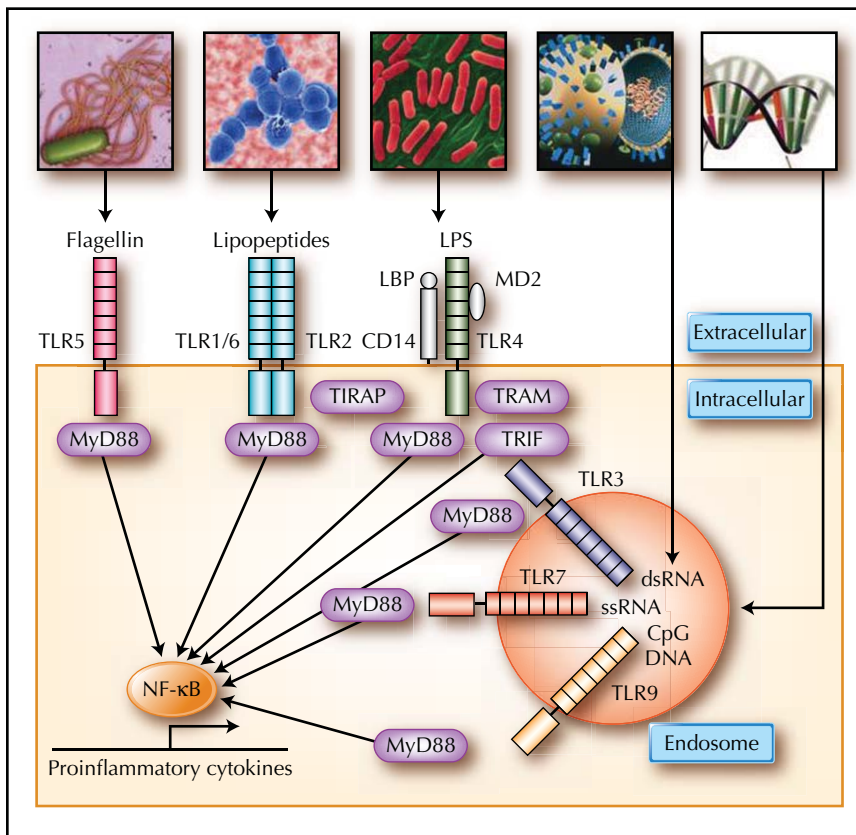
Sepsis is clinically defined as an infection with evidence of systemic inflammation, as reflected by increased or decreased temperature or leukocyte count, tachycardia, and rapid breathing [1,2•]. This formal definition tries to cover the clinical syndrome that results from an overwhelming systemic host response to infection [1,2•]. Both the incidence of sepsis and the number of sepsis-related deaths are increasing: in the United States the incidence of sepsis is 240 per 100,000 population, making sepsis the 10th leading cause of death overall [3]. The increased use of invasive procedures, immunosuppressive therapy, chemotherapy, and organ transplantation, as well as the HIV epidemic and increasing microbial resistance are all recognized as potential reasons for the increased incidence of sepsis [3]. One problem with clinical trials of novel sepsis therapies is that the patients are notoriously heterogeneous with respect to the inciting cause of their disease, the comorbid conditions that define its course, and the acute severity of their initial presentation [4,5]. These major differences among patients in clinical sepsis trials have given rise to a remarkable variety in mortality risks across studies and probably to variable response rates to given interventions [4]. These observations and the failure of virtually all clinical sepsis trials have led to a rethinking of the true definition of sepsis. Often, the explanation

of sepsis is oversimplified as just the result of exacerbated inflammatory responses. A 2003 consensus meeting of sepsis experts tried to tackle this problem but concluded that no evidence exists to support changing the original 1992 consensus meeting definitions. The 2003 consensus found that apart from expanding the list of signs and symptoms of sepsis to reflect clinical bedside experience, the lack of evidence underscores the continuing challenge in diagnosing sepsis today [1]. In recent years, exciting advances have been made in understanding sepsis pathogenesis, from the initial recognition of the invading pathogen to the counter-acting host response. These new insights provide us with a steady stream of new potential treatment targets. This review examines the latest trends and developments in the sepsis field and aims to help set the stage for the current debate about whether the sepsis response is good or bad.

## Toll-like Receptors and the Inflammatory Response

### Toll-like receptors and pathogen recognition

Pathogens that attack the host are initially recognized by the innate immune system through pattern-recognition receptors (PRRs) [6]. One family of PRRs, the recently discovered class of Toll-like receptors (TLRs), has emerged as the central line of defense against invading microbes (Fig. 1). TLRs are the first to detect host invasion by pathogens, initiate immune responses, and form the crucial link between the innate and adaptive immune systems [6]. TLRs together with other PRRs enable the innate immune system to discriminate potential pathogens from self by recognizing conserved motifs on pathogens that are not found in higher eukaryotes. Examples of these so-called pathogen-associated molecular patterns (PAMPs), include lipopolysaccharide (LPS) from the outer membrane of gram-negative bacteria, peptidoglycan (present in most bacteria), lipoteichoic acid (in many gram-positive bacteria), and mannans in the yeast cell wall. Ligands for 10 mammalian TLRs have been described (11 in mice). It must be emphasized that the TLRs function in a coordinated manner; different components of one microorganism are recognized by different TLRs. *Escherichia coli*, for example, is a gram-negative bacterium expressing several PAMPs (peptidoglycan, LPS, flagellin, and bacterial DNA), which are all recognized by different TLRs (TLR2, TLR4, TLR5, and TLR9, respectively). Given their central role in the recognition of microbes, it is rational to hypoth-



**Figure 1.** Toll-like receptors (TLR) and pathogen recognition. The TLR family discriminates between specific patterns of microbial components. TLR2, which can associate with TLR1 and TLR6, is essential for the recognition of microbial lipopeptides. TLR4 recognizes lipopolysaccharide (LPS). LPS first binds to LPS-binding protein (LBP), which transfers LPS to CD14. Binding of LPS to CD14 leads to the association of CD14 with MD2 and TLR4. TLR5 is a receptor for flagellin. TLR9 is the CpG DNA receptor, whereas TLR3 and TLR7 are implicated in the recognition of viral double-stranded RNA (dsRNA) and single-stranded RNA (ssRNA), respectively. After TLR stimulation, the adaptor molecule myeloid differentiation primary-response protein 88 (MyD88) is recruited. This will lead to the release of nuclear factor (NF)- $\kappa$ B, which will result in the transcription of a whole range of inflammatory genes. Next to MyD88, the adaptor molecules Toll/interleukin receptor (TIR) domain-containing adaptor protein (TIRAP), TIR domain-containing adaptor protein-inducing interferon- $\beta$  (TRIF), and TRIF-related adaptor molecule (TRAM) have been identified. TIRAP is essential for MyD88-dependent signaling through TLR2 and TLR4. TRIF is essential for the TLR3- and TLR4-mediated activation of the MyD88-independent pathway. TRAM is involved in TLR4-mediated MyD88-independent/TRIF-dependent signaling pathways.

esize that TLRs play a central role in sepsis pathogenicity. Indeed, animals lacking the gene encoding TLR4 do not develop shock in response to LPS [6]. Although LPS is the best studied and probably most important mediator of sepsis, peptidoglycan, lipoteichoic acid, bacterial CpG DNA, and flagella are other important microbial products implicated in the pathogenesis of sepsis. All these PAMPs signal through different TLRs. As a result, the relationship between TLR expression and human sepsis is complex.

In recent years, TLR2 has been recognized as the gram-positive TLR because of its ability to sense major gram-positive cell wall components such as peptidoglycan and lipoteichoic acid, whereas TLR4, the LPS receptor, is seen as the gram-negative TLR. However, as more knowledge about the precise role TLRs in different bacteria becomes available, this concept should be modified. For instance, *Streptococcus pneumoniae* is sensed by the innate immune system, not only through TLR2, which recognizes lipoteichoic acid and peptidoglycan, but also through TLR4, which recognizes pneumolysin. It was recently shown that TLR2 is indispensable for alveolar macrophage responsiveness toward *S. pneumoniae* [7]. However, in the same study, TLR2 gene-deficient mice intranasally inoculated with nonlethal to lethal doses of *S. pneumoniae* displayed only a modestly reduced inflammatory response in their lungs and showed an unaltered antibacterial defense and survival in comparison with

wild-type mice [7]. These data suggest that the function of TLR2 in the innate immune response to *S. pneumoniae* is limited. Clearly, other PRRs play an important role.

The LPS-TLR4 interaction appears to be of eminent importance for the induction of an adequate immune response, as illustrated by an impaired host defense of TLR4-deficient mice during gram-negative infection [8,9]. Overall, given their central role in the recognition of microbes, TLRs clearly play a crucial role in sepsis. In this respect, one must consider that on one hand, TLRs are essential for the early detection of pathogen, but on the other hand, they may also cause excessive inflammation after uncontrolled stimulation. TLRs may further contribute to the pathogenesis of sepsis by amplifying inflammatory responses by interaction with endogenous mediators released during injurious processes such as trauma, ischemia, or necrosis. For the recognition of such endogenous danger signals, which have been named alarmins or danger-associated molecular patterns, TLR4 seems to be of particular importance [10].

#### Cytokines and systemic inflammatory response

Activation of TLRs and other PRRs will result in the release of a multitude of cytokines, which have a prime role in the pathogenesis of sepsis by coordinating a wide variety of inflammatory reactions at the tissue level and influencing the production and activity of each other.

Classic proinflammatory cytokines such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)- $\alpha$ , IL-12, IL-15, and IL-18 will activate both humoral and cellular host defense mechanisms. Anti-TNF- $\alpha$  treatment reduces mortality in primate models of overwhelming sepsis induced by intravenous administration of bacteria [11]. In addition, neutralization of IL-1 also reduced lethality in animal models of sepsis [12]. However, subsequent clinical sepsis trials targeting these “magic bullets” such as TNF- $\alpha$  and/or IL-1 failed to demonstrate a clinical benefit in patients with sepsis. These failures likely are related to multiple factors. In this respect, it is good to realize that the primate sepsis model (intravenous infusion of high doses of bacteria) used in the preclinical phase of several immunomodulatory sepsis drugs does not mimic human sepsis in the intensive care unit. In addition, local activity of proinflammatory cytokines at the site of the infection contributes to host defense in experimental models of the two most common causes of sepsis, pneumonia and peritonitis [13].

### C5a and the complement pathway

The complement system, which consists of approximately 30 plasma proteins, can be activated by three different pathways, the classical, alternative, and lectin-binding pathways, all of which lead to cleavage of C3 and C5 into the powerful proinflammatory peptides C3a and C5a [14•]. Although the complement system has traditionally been viewed as an essential part of the host defense against invading microbes, complement activation has recently been implicated in the pathogenesis of sepsis [14•]. In sepsis, the appearance of C5a in the blood indicates a loss of control of complement activation, leading to degradation of the innate immune defenses [14•]. The important role of C5a in sepsis pathogenesis has been underlined by recent studies in rodents: C5 gene-deficient mice show less inflammation upon stimulation with LPS compared to wild-type mice [14•], and treatment with anti-C5a antibodies partially protected rats from cecal ligation and puncture (CLP)-induced sepsis [15].

### Counter-inflammatory Response

The proinflammatory response in sepsis, induced by the initial recognition of the invading pathogens by TLRs, is balanced by a counter-regulatory response that tries to restore immunologic equilibrium. This counter-inflammatory response includes among others a vast system of negative regulators of TLR signaling, a shift from inflammatory (T-helper 1) to anti-inflammatory (T-helper 2) cytokine production, together with apoptosis of immune effector cells, resulting in a well-orchestrated suppression of the immune system [16].

### Negative regulators of the TLR-signaling cascade

The entire TLR family signals via four adapter proteins (ie, myeloid differentiation primary response protein 88

[MyD88], Toll/IL-1 receptor [TIR] domain-containing adaptor protein, TIR domain-containing adaptor protein inducing interferon- $\beta$  [TRIF], and TRIF-related adaptor molecule [TRAM]), which together take care of the response to a whole universe of microbial molecules (Fig. 1) [6]. MyD88 is involved in the signaling of all TLRs except TLR3. After TLR stimulation, MyD88 associates with IL-1 receptor-associated kinase (IRAK) 4, resulting in the phosphorylation of IRAK1. Negative regulation of this TLR signaling pathway is essential [17]. In the cytoplasm, IRAK-M inhibits the dissociation of the IRAK1-IRAK4 complex from the receptor, suppressor of cytokines signaling-1 probably directly inhibits IRAK1, and a short form of MyD88 blocks the association of IRAK4 with MyD88. On the cell membrane, other members of the TIR superfamily such as single immunoglobulin IL-1 receptor-related molecule and ST2 also negatively modulate TLR signaling [18,19]. Other mechanisms by which TLR signaling can be controlled include the reduction of TLR expression by TLR degradation or inhibition by anti-inflammatory cytokines. Furthermore, TLRs clearly can function as death receptors; this TLR-induced apoptosis may be important in the control of a dysregulated TLR response [17].

### Immunoparalysis and apoptosis

In clinical sepsis, the early host response, which is characterized by hyperinflammation, is followed by a phase of hyporesponsiveness and immunodepression (also referred to as immunoparalysis). Important cytokines with mostly anti-inflammatory profiles are IL-1 receptor-antagonist, IL-4, IL-10, and transforming growth factor- $\beta$ , as well as soluble TNF receptors. Monocytes, granulocytes, and lymphocytes of patients with sepsis show a diminished responsiveness after restimulation with bacterial antigens, as indicated by a diminished cytokine release [16,20]. Although immunoparalysis has been regarded as beneficial in the sense that it counteracts a potentially devastating proinflammatory response, it can also lead to an inability to clear infection and a subsequent predisposition to nosocomial infection [16].

Recent work has gained insight into the mechanisms of immune suppression in sepsis. The mentioned shift to anti-inflammatory cytokines is an important factor. Furthermore, Hotchkiss et al. [21•] have shown that large numbers of lymphocytes and gastrointestinal epithelial cells die by apoptosis during sepsis. By committing suicide, these immune cells probably dampen the inflammatory response by simply reducing the amount of circulating immune cells and inducing the release of anti-inflammatory cytokines. Prevention of lymphocyte apoptosis improves the likelihood of survival in animal models of sepsis, illustrating the importance of lymphocyte depletion in this syndrome [16,22,23].

### Vagus nerve and the nicotinic anti-inflammatory pathway

Another physiologic anti-inflammatory mechanism that has recently emerged as an important control system of

the inflammatory response is the vagus nerve. This cranial nerve that innervates most of the peripheral organs can downregulate inflammation by decreasing the release of TNF- $\alpha$ , IL-1, IL-6, and high-mobility group box (HMGB) 1 protein by LPS-stimulated macrophages [24]. This anti-inflammatory effect is mediated by an interaction between acetylcholine, the principal neurotransmitter of the vagus nerve, and the  $\alpha 7$ -nicotinic acetylcholine receptors on macrophages [24,25]. In studies of experimental endotoxemia in rats, surgical dissection of the vagus nerve led to enhanced systemic TNF- $\alpha$  production and accelerated the development of shock. In turn, electrical stimulation of the vagus nerve downregulated TNF- $\alpha$  production and protected the animals from hypotension [24].

Excitingly, treatment with nicotine, which is a ligand for the  $\alpha 7$ -nicotinic acetylcholine receptor, reduced circulating TNF- $\alpha$  and HMGB-1 levels and improved survival in experimental sepsis in rodents [24,25,26•]. Further evidence for the role of the vagus nerve as an anti-inflammatory mediator in sepsis comes from a murine study in which the cytokine release in septic peritonitis was enhanced after previous vagotomy and decreased after nicotine pretreatment [27]. Central muscarinic receptors within the brain play a role in activating the cholinergic anti-inflammatory pathway [28]. Moreover, the spleen is an essential peripheral part of the cholinergic anti-inflammatory reflex [29]. Together, these preclinical data suggest that stimulation of the vagus nerve and/or pharmacologic  $\alpha 7$  cholinergic receptor agonists may be a useful strategy in the treatment of the severe inflammation accompanying sepsis.

## Dysbalance between Coagulation and Anticoagulation

Activation of the coagulation pathway is an important event in the pathogenesis of sepsis. Activation of coagulation and deposition of fibrin as a consequence of inflammation can be considered instrumental in containing inflammatory activity to the site of infection. However, inflammation-induced coagulation may be detrimental in those circumstances when the triggered blood coagulation system is insufficiently controlled, which can lead to the clinical syndrome of disseminated intravascular coagulation and microvascular thrombosis [30,31]. A simplified overview of the interactions between coagulation and inflammation is presented in Figure 2 [31].

### Tissue factor and activation of coagulation

Tissue factor (TF) is constitutively expressed by different cell types in the extravascular compartment (eg, pericytes, cardiomyocytes, smooth muscle cells, and keratinocytes), whereas monocytes and endothelial cells will only start expressing TF during severe inflammation [30,31]. TF is one of the primary initiators of the inflammation-induced coagulation cascade [30,31]. Interaction of TF with factor VIIa, which circulates at low levels in the bloodstream,

results in the activation of factor X either directly or indirectly through the activation of factor IX. Activated factor X converts prothrombin (factor II) to thrombin, which finally induces the conversion of fibrin to fibrinogen, thereby inducing the formation of a blood clot.

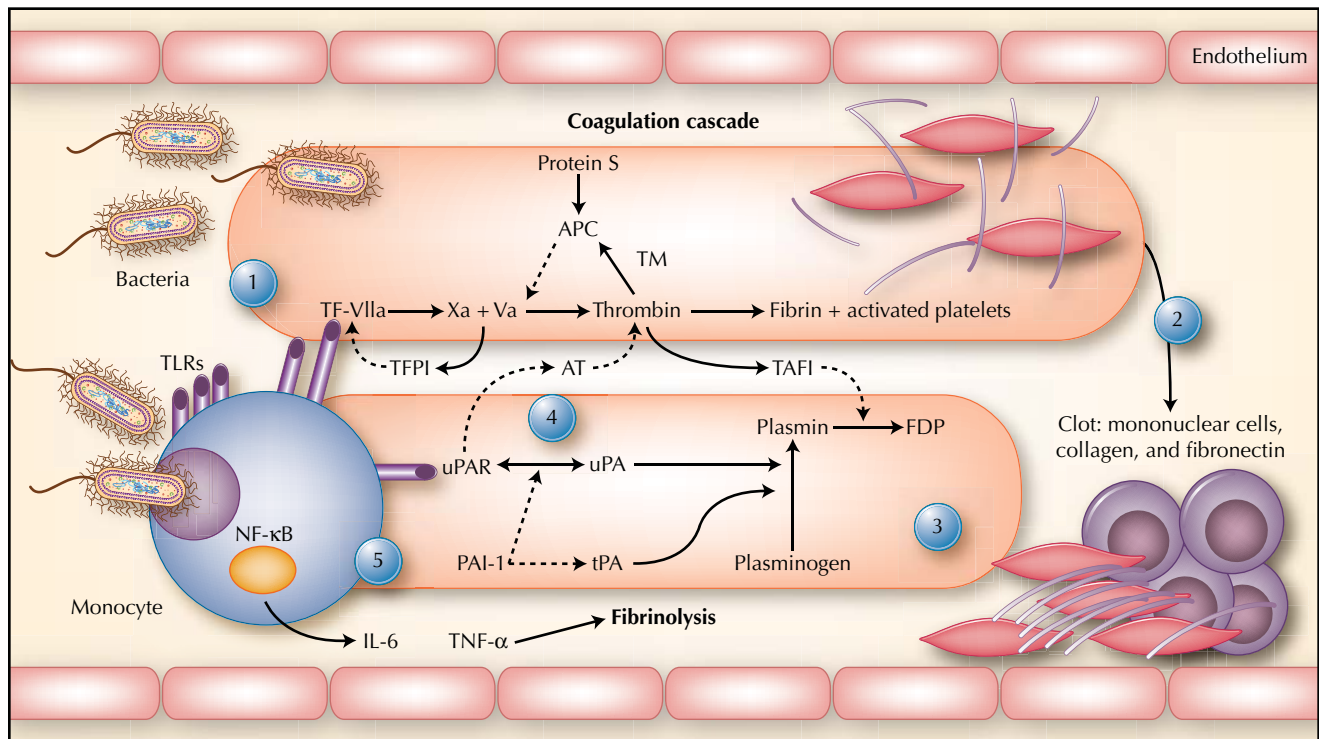
The pivotal role of TF in activation of coagulation during sepsis has been established by many different experiments. The generation of thrombin in humans intravenously injected with a low dose of endotoxin, documented by a rise in the plasma concentrations of the prothrombin fragment F1+2 and of thrombin-antithrombin complexes, was preceded by an increase in TF messenger RNA levels in circulating blood cells, enhanced expression of TF on circulating monocytes, and the release of TF-containing microparticles [32,33]. A number of different strategies prevent the activation of the VIIa-TF pathway in endotoxemic humans and chimpanzees and abrogate the activation of the common pathway of coagulation in bacteremic baboons. In healthy humans injected with LPS, intravenous infusion of recombinant TF pathway inhibitor (TFPI) caused a dose-dependent inhibition of coagulation activation [34]. Strategies that potentially inhibited coagulation activation in endotoxemic or bacteremic primates include antibodies directed against TF or factor VII/VIIa and TFPI [30,31,35,36].

### Anticoagulant mechanisms

Activation of coagulation and the resulting generation of fibrin is counterbalanced by anticoagulant mechanisms, in particular TFPI, antithrombin, activated protein C (APC), and the fibrinolytic system [30,31]. TFPI is a protease inhibitor primarily produced by endothelial cells that inactivates factor VIIa bound to TF. Antithrombin inhibits factor Xa, thrombin, and factor IXa, as well as factor VIIa bound to TF. The protein C system provides important control of coagulation by virtue of the capacity of APC to inactivate factors Va and VIIIa, thereby preventing the procoagulant activities of factors Xa and IXa. Protein S serves as an essential cofactor for APC. In the protein C system, thrombin functions as an anticoagulant. This pathway is triggered when thrombin binds to the endothelial cell receptor thrombomodulin [30,37]. Thrombomodulin inhibits coagulation by conversion of thrombin into an activator of protein C via the endothelial protein C receptor.

Several preclinical studies have supported the anticoagulant potencies of TFPI, antithrombin, and the protein C system in vivo. Infusion of either TFPI, antithrombin, or APC attenuated consumptive coagulopathy in septic primates [35,38,39], and inhibition of activation of endogenous protein C by a monoclonal antibody exacerbated the response to a lethal *E. coli* infusion [39]. In the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study, in which 1690 patients with severe sepsis were randomized to receive APC or placebo, APC reduced morbidity and mortality [40].





**Figure 2.** Simplified overview of the bidirectional relation between inflammation and coagulation in sepsis. **1**, Invading pathogens are recognized by the immune system through Toll-like receptors (TLRs). After recognition, the coagulation cascade is activated by inducing tissue factor (TF) expression on monocytes and granulocytes. In sepsis, decreased levels of free protein S and activated protein C (APC) are seen, ultimately leading to enhanced thrombin formation. **2**, A fibrin clot with activated mononuclear cells is formed. In severe cases, this may lead to disseminated intravascular coagulation. **3**, The activated counteracting plasmin-mediated fibrinolysis leads to the formation of fibrin degradation products (FDP). **4**, Furthermore, after binding to urokinase plasminogen activator (uPA), the upregulated uPA receptor (uPAR) on monocytes and granulocytes will enhance the fibrinolytic pathway. Plasminogen activator inhibitor (PAI)-1, which is strongly upregulated in sepsis, inhibits these fibrinolytic events. **5**, Binding of among other TF and thrombin to specific protease-activated receptors on inflammatory cells may affect inflammation by inducing release of proinflammatory cytokines, which will further modulate coagulation and fibrinolysis. Straight and dashed arrows indicate stimulatory and inhibitory effects, respectively. IL—interleukin; NF—nuclear factor; TAFI—thrombin activatable fibrinolysis inhibitor; TFPI—tissue factor pathway inhibitor; TM—thrombomodulin; TNF—tumor necrosis factor; tPA—tissue-type plasminogen activator. (Adapted from Wiersinga et al. [31].)

Hemostasis is further controlled by the fibrinolytic system in which plasmin plays a key in the degradation of fibrin. Plasmin is generated from plasminogen by a series of proteases, most notably tissue-type plasminogen activator and urokinase-type plasminogen activator. The main inhibitor of plasminogen activator is plasminogen activator inhibitor (PAI)-1, which binds to tissue-type plasminogen activator and urokinase-type plasminogen activator. Plasma concentrations of PAI-1 are elevated in patients with sepsis and are predictive of unfavorable outcome in sepsis patients [41].

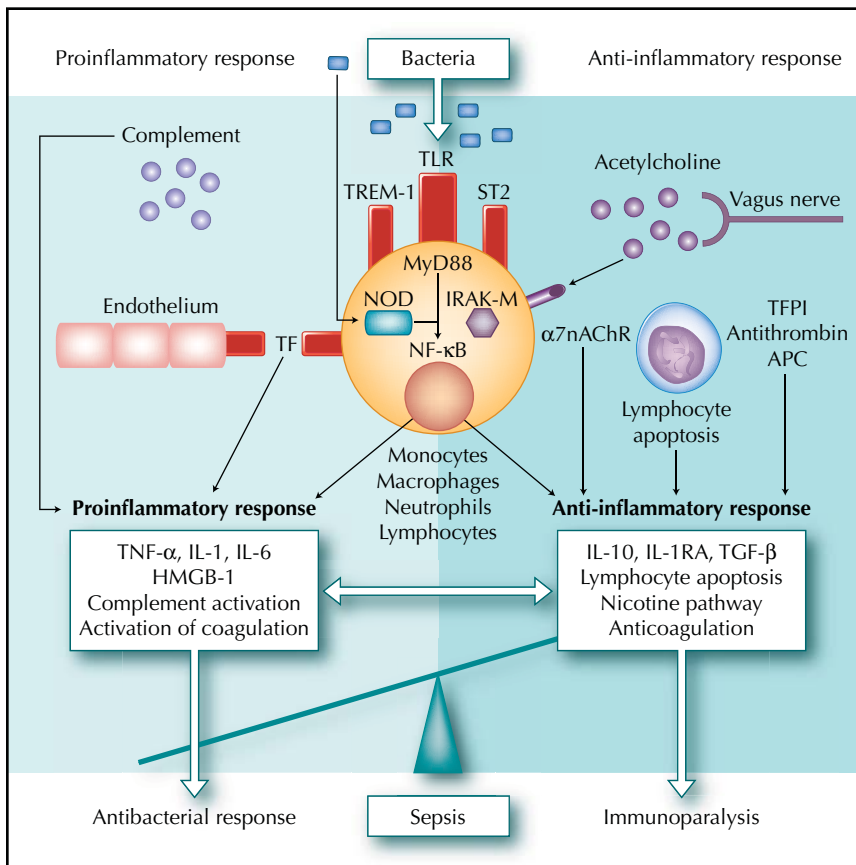
#### Disturbance of the balance between coagulation and anticoagulation

Severe sepsis is characterized by activation of TF-dependent coagulation with concurrent inhibition of anticoagulant mechanisms: TF procoagulant activity is markedly enhanced, whereas the activities of TFPI, anti-thrombin, the protein C–APC system, and fibrinolysis are all impaired, resulting in a shift toward a net procoagulant state [42]. The impairment of the protein C system during

sepsis is the result of increased consumption of protein S and protein C and decreased activation of protein C by downregulation of thrombomodulin on endothelial cells. Finally, fibrinolysis is impaired in sepsis, primarily due to exaggerated release of PAI-1 [30,31,41].

#### New Actors in the Sepsis Theater High-mobility group box 1 protein

HMGB-1 functions as a late-acting proinflammatory mediator of sepsis, and it circulates in high concentrations in the majority of septic patients [43,44]. It is secreted by activated immune cells and elicits prolonged activation of cells, either directly or more likely indirectly via substances bound to HMGB1, via the receptor for advanced glycation end products, TLR2, and TLR4 [45]. LPS stimulation was found to mediate the expression of HMGB-1 from macrophages at a considerably later stage than the release of the proinflammatory cytokines TNF- $\alpha$  and IL-1 [44]. Administration of HMGB-1 itself is lethal to mice, whereas the administration of antibodies to HMGB-1 attenuated endotoxin lethality



**Figure 3.** Invasion of bacteria and the septic response: the pro- and anti-inflammatory pathways in sepsis. Invading bacteria are recognized by pathogen recognition receptors, such as the Toll-like receptor (TLR) and nucleotide-binding oligomerization domain (NOD) proteins, after which a proinflammatory response is initiated via nuclear factor (NF)- $\kappa$ B. Next to the release of proinflammatory cytokines, the antibacterial response is characterized by activation of both the complement and coagulation systems. Triggering receptor expressed on myeloid cells (TREM)-1 serves as an amplifier of the TLR-initiated inflammatory response. The counteracting anti-inflammatory response is subsequently characterized by negative regulators of the TLRs such as ST2, the release of anti-inflammatory cytokines, apoptosis of lymphocytes, activation of the nicotinic anti-inflammatory pathway, and the release of anticoagulant proteins. Eventually, the balance between the pro- and anti-inflammatory reactions will determine the outcome of the septic response.  $\alpha$ 7nAChR— $\alpha$ 7-nicotinic acetylcholine receptor; APC—active protein C; HMGB-1—high-mobility group box 1 protein; IL—interleukin; IL-1RA—IL-1 receptor antagonist; IRAK-M—IL-1 receptor-associated kinase M; MyD88—myeloid differentiation primary-response protein 88; TGF—transforming growth factor; TFPI—tissue factor pathway inhibitor; TNF—tumor necrosis factor.

[44]. As mentioned above, stimulation of the cholinergic anti-inflammatory pathway with nicotine inhibits both LPS- and TNF- $\alpha$ -mediated release of HMGB-1 [26•]. Nicotine attenuates serum HMGB-1 levels, paralleling improved survival in experimental models of sepsis. Of significance, encouraging results were seen in sepsis models, even when anti-HMGB-1 treatment was started at a late stage.

#### Triggering receptor expressed on myeloid cells 1

Triggering receptor expressed on myeloid cells (TREM)-1 amplifies the TLR-mediated inflammatory response to microbial products [46]. TREM-1, which signals through the adaptor protein DAP12, is strongly and specifically expressed on monocytes and neutrophils from patients with sepsis [46]. Of diagnostic importance, high concentrations of plasma-soluble TREM-1 can indicate infection in patients with systemic inflammatory response syndrome [47]. Excitingly, blockade of TREM-1 protects mice against LPS-induced shock, as well as microbial sepsis caused by live *E. coli* or CLP [46]. In addition, a synthetic peptide mimicking a short, highly conserved domain of soluble TREM-1 protected septic animals from hyper-responsiveness and death [48•]. Intriguingly, although TREM-1 signals through the adaptor protein DAP12 [46], a recent study showed that DAP12-deficient mice have—contrary to what would be expected—enhanced TLR responses in vitro, as indicated

by an enhanced production of proinflammatory cytokines of DAP12-deficient macrophages in response to TLR agonists, and in vivo, as indicated by an increased susceptibility to endotoxic shock [49]. Perhaps certain DAP12-associated receptors function as negative regulators of TLR responses.

#### Macrophage migration inhibitory factor

In recent years, macrophage migration inhibitory factor (MIF) has emerged as a pivotal regulator of innate immunity that has been implicated in sepsis pathogenesis [50,51]. MIF regulates innate immune responses through modulation of TLR4: when MIF-deficient mice are challenged with LPS, they show a defective response as a direct result of decreased TLR4 expression [50]. In patients, MIF levels correlate with fatal outcome in sepsis [52]. MIF-directed therapies might offer a new treatment opportunity for sepsis. Inhibition of MIF activity with neutralizing anti-MIF antibodies protected mice from septic shock [51]. Furthermore, a specific small molecule inhibitor of MIF, named ISO-1, partially protected mice from sepsis induced by endotoxin or CLP [53].

#### Conclusions

A careful balance between the inflammatory and anti-inflammatory response is vital in order to survive the daily invasion of pathogens (Fig. 3). Sepsis has always

been regarded as the result of an exacerbated detrimental inflammatory response toward invading bacteria. However, recent insights described in this review have forced us to rethink this sepsis paradigm. Indeed, septic patients can die from the initial exacerbated hyperinflammatory response, but remarkably, most patients will succumb during the following extended period of immunodepression [21•]. Likewise, sepsis will cause triggering of the coagulation system while diminishing the activity of both natural anticoagulant mechanisms and the fibrinolytic system. Augmented interactions between inflammation and coagulation can give rise to a vicious cycle, eventually leading to dramatic events such as those manifested in severe sepsis and disseminated intravascular coagulation. Taken together, one can state that without a good inflammatory response toward invading bacteria, all will succumb; however, too good of a septic response can lead to a fatal outcome.

## Acknowledgment

Dr. Wiersinga is supported by the Dutch Foundation for Tropical Research (WOTRO).

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